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ABSTRACT

Hepatocyte growth factor/scatter factor (HGF/SF), acting through the Met receptor, plays an important role in most human solid tumors and inappropriate expression of this ligandreceptor pair is often associated with poor prognosis. The molecular basis for the malignant activity imparted by signaling of HGF/SF-Met in cancer cells has been attributed to its mitogenic and invasive properties. However, HGF/SF also induces angiogenesis, but the signaling mechanism has not been understood, nor has this activity been directly associated with HGF/SF-Met mediated tumorigenesis. HGF/SF induces expression in vitro of VEGF, a key agonist of tumor angiogenesis. By contrast, thrombospondin-1 (TSP-1) is a negative regulator of angiogenesis. This application discloses that, in the very same tumor cells, in addition to inducing VEGF expression, HGF/SF dramatically down regulates TSP-1 expression. TSP shut off plays an important, extrinsic role in HGF/SF-mediated tumor development, as ectopic expression of TSP-1 markedly inhibited tumor formation through the suppression of angiogenesis. While VEGF induced expression is sensitive to inhibitors of several pathways, including MAP kinase, PI3 kinase and Stat3, TSP-1 shut off by HGF/SF is prevented solely by inhibiting MAP kinase activation. Thus HGF/SF is a "switch" for turning on angiogenesis. TSP-1 is a useful antagonist to tumor angiogenesis, and therefore TSP-1 and agonist peptides and mimics, as well as inducers of TSP-1, have therapeutic value when used in conjunction with inhibitors of VEGF.

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